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AUTHOR(S):

Kawabata, Takeo; Wirth, Thomas; Yahiro, Kiyoshi; Suzuki, Hideo; Fuji, Kaoru

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Memory of Chirality: Direct Asymmetric α-Alkylation of Phenylalanine Derivatives

Takeo Kawabata, Thomas Wirth, Kiyoshi Yahiro, Hideo Suzuki, and Kaoru Fuji

The (*S*)-phenylalanine derivative 1 was treated with lithium 2,2,6,6-tetramethylpiperidide and then with methyl iodide at -78 °C to afford **3** in 82% ee without addition of any external chiral source. The asymmetric methylation reaction proceeded with retention of configuration.

Keywords: Asymmetric synthesis/ Amino acid/ Alkylation

Asymmetric synthesis of a-substituted α-amino acids has attracted considerable attention because of the biological and chemical importance of these compounds.[1] One of the most efficient methods for their synthesis has been *via* enolate chemistry utilizing chiral auxiliaries. However, it would be even more efficient if direct α-alkylation of the enolates generated from optically active α-amino acids could proceed enantioselectively without using any external chiral source. This has not been possible due to the loss of chirality at the α-carbon of α-amino acids in the corresponding enolates due to their achiral nature. However, enolates generated from optically active α-amino acids are not always achiral, according to the concept of *memory of chirality*, which we recently proposed.[2] In searching for conditions under which enolates are chiral, we discovered that optically active *N*-methyl-*N*-Boc-phenylalanine derivatives can undergo direct asymmetric α-alkylation with ee's as high as 82% without the addition of any external chiral source.

Treatment of **1** (>96% ee) with a variety of bases in THF followed by methyl iodide afforded **3**, whose ee was determined as its *N*-benzoyl derivative **4** (Table I). Among the bases screened, lithium 2,2,6,6-tetramethylpiperidide (LTMP) proved to be the most effective for the asymmetric induction (entries 1-4). Asymmetric methylation proceeded with retention of configuration when LTMP or lithium diisopropylamide (LDA) was employed, while inversion of configuration was observed with potassium hexamethyldisilazide (KHMDS). The absolute configuration of **3** was determined by chemical correlation with **5**. The degree of asymmetric induction depended on the amount of LTMP employed (entries 5-9). The best results (82% ee, 40% yield) were obtained when 1.0 eq of LTMP was employed. Increasing the amount of base decreased the efficiency of the asymmetric induction without affecting the yield of **3**. Deuteration of the enolate generated from **1** and 1.1 eq of LTMP was carried out by treatment with D_2O. Recovered **1** (76% yield) contained 51% deuterium and had 76% ee with *S* configuration. If all of the enolate was trapped with

SYNTHETIC ORGANIC CHEMISTRY —Fine Organic Synthesis—

Scope of Research

Fundamental studies are being made for creation of new functional materials with novel structures and properties and for utilization of high pressure in organic synthesis. The major subjects are: synthetic and structural studies on novel cyclic p-systems; chemical transformation of fullerene C60; utilization of carbon monoxide and dioxide for organic synthesis under the transition-metal catalysis

Prof
FUJI,
Kaoru
(D Pharm Sc)

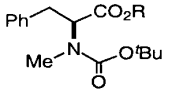
Assoc Prof
TANAKA,
Kiyoshi
(D Pharm Sc)

Instr
KAWABATA,
Takeo
(D Pharm Sc)

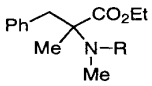
Techn
TERADA,
Tomoko

Secretary
TAKEDA, Kyoko
Guest Scholar
POOLSAK, Sahakitpicnan
Guest Research Associate
AHN, Mija; LAKSHMAIAH, Gingipalli; CHEN, Jijun
Students
NAGATO, Minoru (DC); SUZUKI, Hideo (DC); TAKASU, Kiyosei (DC); FURUTA, Takumi (DC); SHANG, Muhong (DC); TSUBAKI, Kazunori (DC); WATANABE, Toshiyuki (DC); ASAKAWA, Naoyuki (MC); KONDOH, Masakatu (MC); WATANABE, Yukari (MC); OHNISHI, Hiroshi (MC); HAMADA, Masaki (MC); MORIYAMA, Shoko (MC); OHTSUBO, Tadamune (UG); TAKAOKA, Hiromi (UG); YAMAMOTO, Kensaku (UG); YOSHIDA, Masato (UG)
Research Fellow
HAMAJIMA, Yoshio; WATANABE, Joshu
Research Student
KOYAMA, Naohisa; NURUZZAMAN,Mohammad

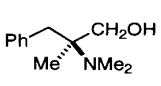
deuterium, deuteration would proceed with retention of configuration in 55% ee. Enolate formation was estimated to be complete in entries 7-9 since the ee of recovered **1** was ~ 50%, whereas enolate formation in entries 5 and 6 was found to be incomplete. When the extent of enolate formation was low, a considerable amount of starting material was recovered (entry **5**). When it was high, on the other hand, formation of side products increased. As a result, a-methylation of **1** proceeded with ~40% yield, irrespective of the extent of enolate formation.



1 : R = Et
2 : R = ^{n}Bu



3 : R=$CO_2{}^t$Bu
4 : R=COPh



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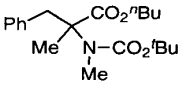

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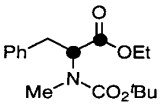

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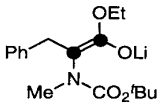

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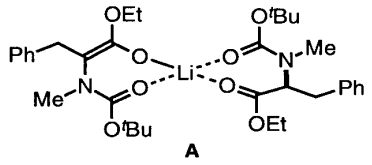
Mechanistic aspects of the present asymmetric induction were investigated. Shown in Chart I are plausible intermediates: (**A**) mixed aggregates of the *achiral* enolate with the undeprotonated optically active starting material, (**B**) a configurationally stable carbanion stabilized by the adjacent *N*-Boc group, (**C**) an enolate with chiral nitrogen strongly coordinated with lithium, (**D**) an enolate with a C-N chiral axis in which the steric bulk of the OLi group is increased by coordination with the amine originating from LTMP, and (**E**) an enolate with a chiral plane. To estimate the feasibility of **A**, cross-over experiments between **1** and the butyl ester **2** were done. A 1 : 1 mixture of **1** (96% ee) and racemic **2** was treated with LTMP (1.0 eq to the total amount of **1** and **2**) at -78 °C followed by addition of methyl iodide at the same temperature to afford optically active **3** (74% ee, 26% yield) and racemic **6** (30% yield). The same treatment of a 1 : 1 mixture of racemic **1** and optically active **2** (96% ee) afforded racemic **3** (17% yield) and optically active **6** (71% ee, 24% yield). These observations clearly indicate that **A** does *not* make a significant contribution to the asymmetric induction.

Table 1. Asymmetric α-Methylation of **1**.[a]

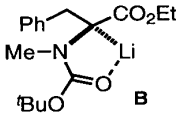
entry	base (eq)	yield of **3**	ee of **4**[b]	recovered **3**	
				yield	% ee[c]
1	LTMP (1.1)	38	79 (*S*)	23	87
2	LDA (1.2)	57	22 (*S*)	25	*d*
3	LHMDS (1.2)	0	-	*d*	*d*
4	KHMDS (1.2)	79	20 (*R*)	0	-
5	LTMP (1.0)	40	82 (*S*)	36	92
6	LTMP (1.5)	42	77 (*S*)	17	73
7	LTMP (2.0)	42	73 (*S*)	13	48
8	LTMP (4.0)	36	66 (*S*)	13	54
9	LTMP (6.0)	37	55 (*S*)	22	48

[a]**1** (98% ee) was treated with the base in THF at -78 °C for 15 min followed by methyl iodide at -78 °C for 4 h. [b]Determined by HPLC analysis using Daicel CHIRALPAK AS (3% EtOH/hexane). The letter in the parentheses indicates the absolute configuration. [c]The absolute configuration was S in each entry. Ee was determined by HPLC analysis using Daicel CHIRALPAK AS (3% EtOH/hexane). [d]Not determined.

Chart I



A



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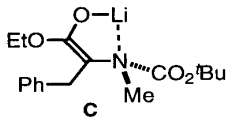
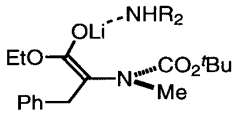


C



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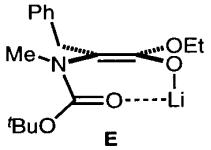

E

The anionic species generated from **1** and LTMP can be expected to contain some chiral information. To examine the structure of the anionic species, the ^{13}C-NMR spectrum was studied on the anionic species generated from [1,2-$^{13}C_2$]-phenylalanine derivative **7** (racemic) with ^{7}Li-LTMP (1.7 eq) in d_8-THF at -78 °C. Although the spectrum measured at this temperature gave complicated and uninterpretable signals, raising the temperature of the solution to 20 °C induced a complete change in the spectrum, in which two doublets now appeared at d 159.9 (J = 115 Hz) and 86.4 (J = 115 Hz). These signals could be assigned to a normal enolate structure **8**. Re-cooling the enolate solution to -78 °C did not lead to significant changes in the spectrum, the major signals of **8** remaining unchanged. Next, we investigated the effects of the observed structural changes caused by temperature variation on the asymmetric a-methylation of **1**. Racemic **3** was obtained in 26% yield when **1** (96% ee) was treated with LTMP (1.0 eq) at -78 °C for 15 min, then at 20 °C for 45 min followed by methyl iodide at -78 °C. Thus, it can be concluded that the initially formed anionic species at -78 °C could memorize the original chiral information, while the achiral enolate **8**, formed after raising the temperature, neither possessed chiral information nor could recall it even when re-cooled to -78 °C. Studies directed toward structure determination of the intermediary anionic species generated from **1** and LTMP at -78 °C are currently under way.

References and Notes

1. a) For examples, see: a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. J. *Am. Chem. Soc*. **1983**, *105*, 5390. b) Schöllkopf U. *Tetrahedron* **1983**, *39*, 2085.
2. Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, 113, 9694.